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Frank C. Eisenschenk
Frank C. Eisenschenk, Ph.D., Patent Attorney

REQUEST FOR CERTIFICATE OF
CORRECTION UNDER 37 CFR 1.322
AND UNDER 37 CFR 1.323
Docket No. MET-075T
Patent No. 7,371,857

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Kanda Ramasamy, Jean-Luc Girardet, Haoyun An, Zhi Hong, Robert Orr
Issued : May 13, 2008
Patent No. : 7,371,857
For : Synthesis for Hydroxyalkylated Heterocyclic Bases

Mail Stop Certificate of Corrections Branch
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REQUEST FOR CERTIFICATE OF CORRECTION
UNDER 37 CFR 1.322 (OFFICE MISTAKE)
UNDER 37 CFR 1.323 (APPLICANT MISTAKE)

Sir:

A Certificate of Correction for the above-identified patent has been prepared and is attached hereto.

In the left-hand column below is the column and line number where errors occurred in the patent. In the right-hand column is the page and line number in the application where the correct information appears.

Patent Reads:

Column 4, line 64:

“—NH₃+”)”

Application Reads:

Page 6, line 2:

-- —NH₃⁺)--

Patent Reads:Column 10, line 39:“R₁ is NH₂;**Patent Reads:**Column 12, line 24:

“W is ethyl group”

Application Reads:Amendment Under 37 CFR § 1.111 dated
December 12, 2007, Page 3:--R₁ is NH₂;**Application Should Read:**Page 18, original claim 17:

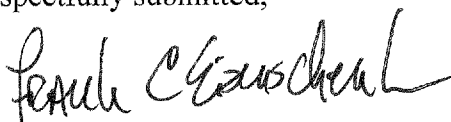
-- W is an ethyl group--.

A true and correct copy of page 6 of the specification as filed and a true and correct copy of Applicants' Amendment Under 37 C.F.R. § 1.111 dated December 12, 2007 which support Applicants' assertion of the errors on the part of the Patent Office accompany this Certificate of Correction.

The fee of \$100.00 was paid at the time this Request was filed. The Commissioner is also authorized to charge any additional fees as required under 37 CFR 1.20(a) to Deposit Account No. 19-0065.

Approval of the Certificate of Correction is respectfully requested.

Respectfully submitted,



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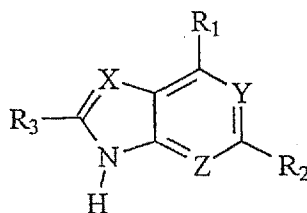
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Attachments: Copy of page 6 of the specification
Copy of Amendment Under 37 C.F.R. § 1.111

(e.g., -OH), non-polar groups (e.g., aryl, alkyl, alkenyl, alkynyl, etc.), ionic groups (e.g., -NH_3^+), halogens (e.g., -F, -Cl), and all chemically reasonable combinations thereof.

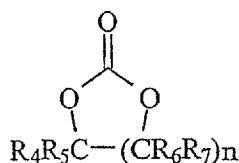
For example, especially suitable heterocyclic bases will have a structure according to **Structure 1**



Structure 1

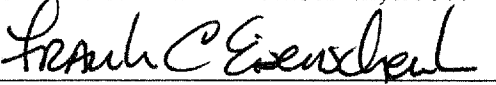
wherein X, Y and Z are independently N or CR, with R being H, halogen, OH, NH₂, or substituted or unsubstituted alkyl, alkenyl, alkynyl, aryl, or alkaryl; wherein R₁, R₂, and R₃ are independently H, halogen, OH, NH₂, CO(NH₂), CNH(NH₂), N₃, or a substituted or unsubstituted alkyl, alkenyl, alkynyl, aryl, or alkaryl. It is still further preferred that the concentration of the heterocyclic base is relatively high. Consequently, and depending on the reaction solvent it is preferred that the concentration of the heterocyclic base may be up to 220mM, and more preferably at least 270mM (especially where dimethylacetamide is the solvent).

Similarly, it should be recognized that the alkylating reagent need not necessarily be limited to ethyl carbonate, and depending on the length and chemical composition, the alkyl portion in the alkyl carbonate may vary substantially. For example, the alkyl portion may include one or more substituents, and may have more than two carbon atoms. Therefore, particularly suitable alkylating reagents will have a structure according to **Structure 2**



Structure 2

I hereby certify that this correspondence is being electronically filed in the United States Patent and Trademark Office on December 12, 2007.


Frank C. Eisenschenk, Ph.D., Patent Attorney

AMENDMENT UNDER 37 C.F.R. § 1.111
Patent Application
Docket No. MET-075T

COPY

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner : Mark L. Berch
Art Unit : 1624
Applicants : Kanda Ramasamy, Jean-Luc Girardet, Haoyun An, Zhi Hong, Robert Orr
Serial No. : 10/523,938
Filed : February 8, 2005
Conf. No. : 9437
For : Synthesis for Hydroxyalkylated Heterocyclic Bases

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313

AMENDMENT UNDER 37 C.F.R. § 1.111

Sir:

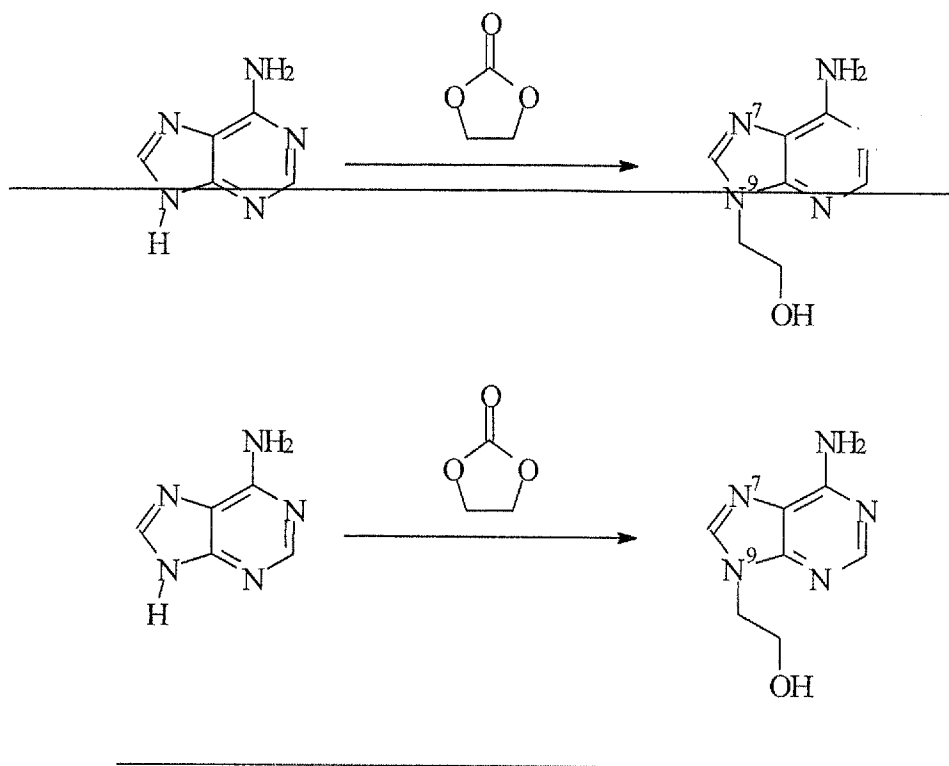
Applicants request that the period for response be extended three months through and including December 12, 2007, the fees for which have been paid at the time this Amendment was filed.

In response to the Office Action dated June 12, 2007, please amend the above-identified patent application as follows:

In the Specification

Please substitute the following paragraph on page 10, beginning at line 1:

The inventors performed numerous reactions between various alkylene carbonates and various heterocyclic bases using selected solvents and predetermined conditions (*e.g.*, with or without catalyst, varied temperature, etc.), to optimize total yield and reaction selectivity (*i.e.*, selectivity of the alkylation towards the N9 nitrogen over other position, and especially over the N7 nitrogen where present) of the alkylation reaction between ethylene carbonate and adenine as depicted in Scheme 2 below.



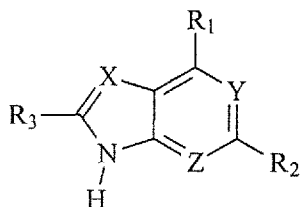
Scheme 2

Please replace original Figures 1-3 with the attached new Figures 1-3.

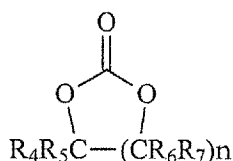
In the Claims

1 (currently amended). A method of preparing a compound according to Structure 3 comprising:

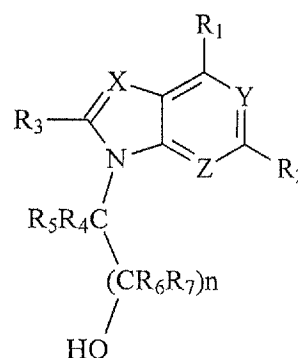
reacting a heterocyclic base according to Structure 1 with a compound according to Structure 2 in dimethylacetamide to form a product according to Structure 3;



Structure 1



Structure 2



Structure 3;

wherein X, Y and Z are ~~independently N or CR, with R being H, halogen, OH, NH₂, or substituted or unsubstituted alkyl, alkenyl, alkynyl, aryl, or alkaryl;~~

wherein R₁ is NH₂;

wherein R₂ is H;

wherein R₃ is H;

wherein R₄, R₅, R₆, and R₇ are independently H, halogen, OH, NH₂, CO(NH₂), CNH(NH₂), N₃, or substituted or unsubstituted alkyl, alkenyl, alkynyl, aryl, or alkaryl;

wherein n is an integer between 1 and 3; and

isolating Structure 3 from the dimethylacetamide solvent using isopropanol or tert-butylmethylether.

2 (canceled).

3 (original). The method of claim 1 wherein R_4 , R_5 , R_6 , and R_7 are H, and wherein n is 1.

4 (original). The method of claim 1 wherein Structure 3 is isolated from the dimethylacetamide solvent using isopropanol.

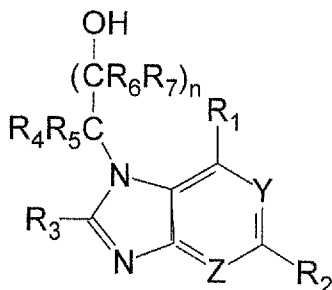
5 (original). The method of claim 1 wherein the step of reacting includes heating of the heterocyclic base according to Structure 1 and the compound according to Structure 2 to a temperature of no less than 150 centigrade.

6 (original). The method of claim 1 wherein the step of reacting includes heating of the heterocyclic base according to Structure 1 and the compound according to Structure 2 to a temperature of no less than 160 centigrade.

7 (original). The method of claim 1 wherein the step of reacting is performed in the presence of a basic catalyst.

8 (original). The method of claim 7 wherein the basic catalyst is NaOH.

9 (original). The method of claim 1 wherein X is N, and wherein the step of reacting the heterocyclic base according to Structure 1 with the compound according to Structure 2 further leads to an N7-alkylated byproduct according to Structure 4



Structure 4.

10 (original). The method of claim 9 wherein the step of reacting the heterocyclic base with the compound gives a total yield of the product and the N7-alkylated byproduct of at least 82%, and wherein about 98% of the total yield is the product and wherein about 1% of the total yield is the N7-alkylated byproduct.

11 (original). The method of claim 9 wherein the step of reacting the heterocyclic base with the compound gives a total yield of the product and the N7-alkylated byproduct of at least 87%, and wherein about 97% of the total yield is the product and wherein about 1.1% of the total yield is the N7-alkylated byproduct.

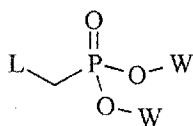
12 (original). The method of claim 9 wherein the step of reacting the heterocyclic base with the compound gives a total yield of the product and the N7-alkylated byproduct of at least 91%, and wherein about 97% of the total yield is the product and wherein about 1.3% of the total yield is the N7-alkylated byproduct.

13 (original). The method of claim 1 wherein the heterocyclic base is present in the dimethylacetamide at a concentration of up to 220mM.

14 (original). The method of claim 1 wherein the heterocyclic base is present in the dimethylacetamide at a concentration of up to 270mM.

15 (canceled).

16 (currently amended). The method of claim 1 further comprising reacting the product according to Structure 3 with a phosphonate ~~claim 15 wherein the phosphonate has a structure according to Structure 5~~



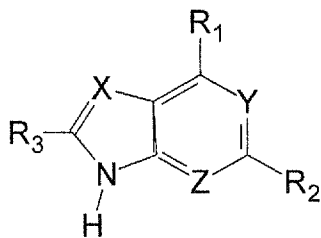
Structure 5

wherein L is a leaving group, and wherein W is a protecting group of the oxygen.

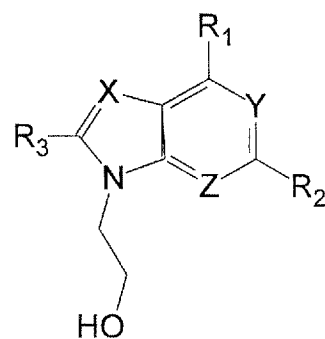
17 (original). The method of claim 16 wherein L is a tosyl group and wherein W is ethyl group.

18 (withdrawn). A method of preparing a compound according to Structure 3 comprising:

reacting a heterocyclic base according to Structure 1 in dimethylacetamide with ethylene oxide to form a product according to Structure 3;



Structure 1



Structure 3

wherein X, Y and Z are independently N or CR, with R being H, halogen, OH, NH₂, or substituted or unsubstituted alkyl, alkenyl, alkynyl, aryl, or alkaryl; and

wherein R₁, R₂, and R₃ are independently H, halogen, OH, NH₂, CO(NH₂), CNH(NH₂), N₃, or substituted or unsubstituted alkyl, alkenyl, alkynyl, aryl, or alkaryl; and

reacting the product according to Structure 3 with a phosphonate to obtain an antiviral nucleoside analog.

19 (currently amended). ~~The method of claim 17 wherein of claim 1 wherein Structure 3 is isolated from the dimethylacetamide solvent using tert-butylmethylether the solvent is dimethylacetamide.~~

Remarks

Claims 1-19 are pending in the subject application. Applicants hereby affirm their election of the invention of Group I (claims 1-17 and 19) with traverse. Applicants acknowledge that claim 18 has been withdrawn from further consideration as being drawn to a non-elected invention. By this Amendment, Applicants have canceled claims 2 and 15 and amended claims 1, 16, and 19. Support for the amendments can be found throughout the subject specification and in the claims as originally filed (see, for example, claims 1 and 2). Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 1-19 are currently before the Examiner (with claim 18 standing withdrawn). Favorable consideration of the pending claims is respectfully requested.

As an initial matter, Applicants gratefully acknowledge the Examiner's indication that claim 2 is objected to but would be allowable if rewritten into independent form to include the limitations of any base and intervening claims.

Claims 15, 17, and 19 are rejected under 35 U.S.C. § 112, second paragraph, as indefinite. Applicants respectfully assert that the claims as filed are definite. However, in an effort to advance prosecution, claim 15 has been canceled. Thus, it is respectfully submitted that this rejection is now moot. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph, is respectfully requested.

Claims 15, 17, and 19 are rejected under 35 U.S.C. § 112, first paragraph, as nonenabled by the subject specification. The Office Action indicates that the specification is enabled for the phosphonates of claim 16 but is not enabled for phosphonates generally. Applicants respectfully assert that the claims as filed are enabled. However, in the interest of advancing prosecution in this matter, claim 15 has been canceled. Accordingly, it is respectfully submitted that this rejection is now moot and reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, is respectfully requested.

Claims 1, 3-17, and 19 are rejected under 35 U.S.C. § 112, first paragraph, as nonenabled by the subject specification. The Office Action states that the specification is enabled for X=Y=Z but is not enabled for other heterocycles. The claims have been amended as suggested by the Office Action

and reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, is respectfully requested.

The drawings are objected to under 37 CFR 1.121(d). Specifically, the Office Action states that the shaded portions of Figures 1-3 are illegible. By this Amendment, replacement Figures 1-3 have been provided to clearly show the text. Applicants respectfully assert that no new matter has been added. Entry of the replacement Figures is requested. Accordingly, reconsideration and withdrawal of the objection is respectfully requested.

The specification is objected to because the structure on page 10 is missing a ring atom. Applicants gratefully acknowledge the Examiner's careful review of the subject specification. The specification has been amended to replace Scheme 2 to show the missing "N" atom. Accordingly, reconsideration and withdrawal of the objection is respectfully requested.

Claim 17 is objected to under 37 CFR 1.75(c) as being of improper dependent form for failing to further limit the subject matter of a previous claim. The Office Action indicates that claim 19 recites what the claims already require. With respect to this issue, it appears that the Office Action inadvertently objected to claim 17 while intending to object to claim 19. By way of this response, claim 19 has been amended to indicate that tert-butylmethylether is used to isolate structure 3 from the solvent thus obviating this rejection. Accordingly, reconsideration and withdrawal of the objection to the claim is respectfully requested.

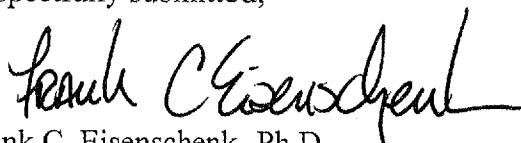
It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicants' agreement with or acquiescence in the Examiner's position. Applicants expressly reserve the right to pursue the invention(s) disclosed in the subject application, including any subject matter canceled or not pursued during prosecution of the subject application, in a related application.

In view of the foregoing remarks and amendments to the claims, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



Frank C. Eisenschenk, Ph.D.

Patent Attorney

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Attachments: Replacement Figures 1-3

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 7,371,857

Page 1 of 1

APPLICATION NO.: 10/523,938

DATED : May 13, 2008

INVENTORS : Kanda Ramasamy, Jean-Luc Girardet, Haoyun An, Zhi Hong, Robert Orr

It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 4,

Line 64, “—NH₃+”)” should read -- —NH₃⁺) --.

Column 10,

Line 39, “R₁ is NII₂;” should read --R₁ is NH₂;--.

Column 12,

Line 24, “W is ethyl group” should read --W is an ethyl group--.

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